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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/680,356	10/06/2003	Chiaki Ishii	58600-8229.US00	5651

79975 7590 11/28/2008

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EXAMINER	
POPA, ILEANA	
ART UNIT	PAPER NUMBER
1633	
MAIL DATE	DELIVERY MODE
11/28/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/680,356	ISHII ET AL.	
	Examiner	Art Unit	
	ILEANA POPA	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18 and 21* is/are pending in the application.

4a) Of the above claim(s) *13-18 and 21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 09/12/2008 has been entered.

Claims 19 and 20 have been cancelled. Claims 13-18 and 21 have been withdrawn. Claims 1-8 have been amended.

Claims 1-12 are under examination.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 1-4, 9, 11, and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Boxer et al. (WO98/23948, of record).

Boxer et al. teach a surface detector array device comprising a substrate defining a plurality of distinct bilayer-compatible surface regions separated by one or more bilayer barrier regions, a bulk aqueous phase covering the substrate surface, a lipid

bilayer expanse carried on each of the bilayer-compatible region, and an aqueous film interposed between each bilayer-compatible region and the corresponding lipid bilayer expanse, i.e., the aqueous film is interposed between the bilayer-compatible surface region and the lower surface of the corresponding bilayer expanse (claims 1 and 9) (p. 4, lines 5-12). Boxer et al. teach that the lipid bilayer expanses have different compositions (claim 3) (p. 4, lines 32 and 33). With respect to the limitation of inner and outer surfaces (claim 1), a bilayer lipid necessarily has inner and outer surfaces; therefore, Boxer et al. do teach lipid bilayer expanses with an inner and an outer bilayer surface (compare also Fig. 1 of the international publication WO98/23948 with Fig. 1 of the instant application, both depicting the same composition). Boxer et al. teach that the bilayer expanses may be modified so that they comprise lipids covalently coupled to biomolecules such as polynucleotides (i.e., oligonucleotide), wherein each bilayer expanse could have a specific biomolecule and wherein the biomolecules can be used to non-covalently attach other biomolecules to the bilayer via specific molecular interactions; i.e., Boxer et al. teach that biomolecules can be attached to the bilayer expanses via specific molecular interactions between complementary oligonucleotides, wherein each expanse comprises a specific oligonucleotide (claims 1 and 4) (p. 4 bridging p. 5, lines 1-5, p. 16, lines 3-21). The bilayer-compatible surface regions may be formed of materials such as SiO_2, MgF_2, CaF_2, and mica (claim 11) and the bilayer expanse may comprise phosphatidylcholine (claim 12) (p. 4, lines 13-15 and 20-24). Boxer et al. also teach that one embodiment relates to sorting devices for biomolecules integrated or attached to the supported bilayer, wherein the device comprises barrier

regions acting as two dimensional sieves having progressively smaller openings that are capable to sort the membrane-associated molecule by size, i.e., the array comprises discrete bilayer patches associated with the lipid bilayer expanses (claim 2) (p. 25 bridging p. 26 and Fig. 5). Since Boxer et al. teach all the limitation of the instant claims, the claimed invention is anticipated by the above-cited art.

Applicant points out that the present claims relate to an array of separated lipid bilayers, wherein the array includes one or more lipids derivatized with an oligonucleotide having a surface region specific sequence and at least one biomolecule anchored to at least one of the lipid bilayer expanses through a complementary oligonucleotide sequence capable of specifically hybridizing with the surface region specific oligonucleotide sequence in that expanse, such that the biomolecule is anchored to that expanse.

Applicant argues that Boxer et al. relate to a surface detector array formed of a substrate having a surface defining a plurality of distinct bilayer-compatible surface regions separated by one or more bilayer barrier regions; the bilayer-compatible surface regions may further include a selected biomolecule covalently or non-covalently attached to a lipid molecule, wherein the biomolecule could be a polynucleotide (see page 4 line 32 through page 5, line 2-5, page 16, line 4). The bilayer may be derivatized with groups or compounds to create a surface having the desired surface exemplified by a ligand bound to the surface of the lipid by attachment to surface lipid components (see page 11, line 32 through page 12, line 2); specific high-affinity molecular interactions

may be employed to link biomolecules to a supported layer (see page 18, lines 7-8). Applicant argues that nowhere do Boxer et al. teach one or more lipids derivatized with an oligonucleotide having a surface region specific sequence. Applicant argues that, although the Examiner points to page 16, lines 3-5 for a teaching that the bilayer may contain receptors or other biomolecules attached to or incorporated into the bilayer, Boxer et al. do not teach that the receptors or the molecules have a surface region specific sequence as in the present claims. Therefore, Applicant submits that Boxer et al. do not disclose each and every element of Applicants' claims and requests the withdrawal of the rejection.

Applicant's arguments are acknowledged however, they are not found persuasive for the following reasons:

Applicant argues that the claims require one or more lipids derivatized with an oligonucleotide having a surface region specific sequence and that Boxer et al. do not teach such a limitation. With respect to this argument, it is noted that claim 1 recites a substrate having a plurality of distinct surface regions, each surface region being associated with a lipid bilyer expanse; each lipid bilayer expanse has "one or more lipids derivatized with an oligonucleotide having a surface region specific oligonucleotide sequence and extending from the outer surface of the associated expanse"; the surface region specific oligonucleotide is used to attach a biomolecule via hybridization with a complementary oligonucleotide coupled to the biomolecule. In other words, claim 1 is drawn to a supported lipid bilayer expanse comprising an oligonucleotide-derivatized lipid with the oligonucleotide extending outward, wherein the oligonucleotide is specific

for the expanse (i.e., the oligonucleotide is used to differentiate between the different expanses on the array) and wherein the oligonucleotide is capable of hybridizing with a complementary oligonucleotide attached to a biomolecule of interest. The recitation of "an oligonucleotide having a region specific oligonucleotide sequence" means nothing more than an oligonucleotide specific for the expanse comprising it. Boxer et al. teach lipid bilayer expanses each comprising lipids covalently coupled to expanse-specific polynucleotides (i.e., a surface region specific sequence) which can be used to non-covalently attach other biomolecules to the bilayer via specific molecular interactions (i.e., hybridization to a complementary polynucleotide); this is exactly what the instant claim 1 recites. For these reasons, it is concluded that Boxer et al. anticipate the instant claims and the rejection is maintained.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1-4 and 9-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boxer et al., in view of each Cornell et al. (U.S. Patent No. 5, 874,316, of record) Arnold et al. (U.S. Patent 5, 310, 648, of record), and Bayerl et al. (U.S. Patent No. 6,051,372, of record).

The teachings of Boxer et al. are applied as above for claims 1-4, 9, 11, and 12. Boxer et al. do not teach the use of self-limiting lateral diffusion to separate the lipid regions from one another (claim 10). However, at the time the invention was made, self-limiting lateral diffusion to separate the lipid regions from one another was taught by the prior art. For example, Cornell et al. teach receptor membranes, wherein the monomers in the membrane may be prevented from diffusing laterally by selecting lipids that are crystalline at room temperature, which eliminates lateral diffusion (column 3, lines 25-29). Arnold et al. teach an imprinted matrix, wherein the spatial organization of molecules in the substrate can be locked into place by a variety of means to form a structure incapable of lateral diffusion, for example by decreasing fluidity (column 7, lines 11-24, column 8, lines 1-10). Bayerl et al. teach patterned surfaces, wherein the lateral diffusion can be prevented by switching the lipid bilayer phase to gel or crystalline and wherein the phase transition can be accomplished by adjusting one physical parameter, the temperature (column 4, lines 25-58, column 5, lines 4-25, column 7, lines 1-24, column 9, lines 32-53). It would have been obvious to one of skill in the art, at the time the indention was made, to maintain the substrate orientation by limiting the lateral diffusion as taught by Cornell et al., Arnold et al., or Bayerl et al., with a reasonable expectation of success. One of skill in the art would have been motivated to do so because the prior art teaches that the use of self-limiting lateral diffusion to keep the lipid regions apart obviates the need for physical barriers on the substrate surface. One of skill in the art would have been expected to have a reasonable expectation of success in using any of the above-mentioned techniques because the art

teaches the successful use of such techniques to limit lateral diffusion between discrete lipid regions. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant argues that none of the secondary references remedies the deficiencies of Boxer et al. Additionally, Applicant argues that, as noted in the reply dated 12/14/2006, each of the cited secondary references describes methods for restricting lateral diffusion rather than self-limiting lateral diffusion, as recited in the instant claims.

Applicant's arguments are acknowledged however, they are not found persuasive for the following reasons:

With respect to Boxer et al., see above. With respect to the argument that made in the reply of 12/14/2006 (i.e., that Cornell et al., Arnold et al., or Bayerl et al. teach restricting lateral diffusion and not self-limiting lateral diffusion), this argument was answered in the final Office action of 5/29/2007. Moreover, the instant specification does not define the term "self limiting lateral diffusion"; all that is required is the absence of physical barriers between the lipid expanses, which is taught by the combination of references above. The lipids of Cornell et al. are crystalline at room temperature (i.e., they do not diffuse at room temperature) and therefore, they exhibit self-limiting lateral diffusion at room temperature; their use overcomes the use of physical barriers between the different lipid expanses. Similarly, the lipids of Arnold et al. and Bayerl et al. exhibit

self-limiting lateral diffusion. For these reasons, the combination of reference above renders the claimed invention *prima facie* obvious,

6. Claims 1-7 and 9-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boxer et al., in view of both Boukobza et al. (J Phys Chem, 2001, 105: 12165-12170, of record) and Niemeyer (DE 19902391, Abstract, of record).

The teachings of Boxer et al. are applied as above for claims 1-4, 9, 11, and 12. Boxer et al. do not teach the biomolecule being a vesicle, second biomolecules associated with the bilayer expanses wherein the second biomolecules are capable of freely moving within the expanse, nor do they teach some of the bilayer expanses as having different second molecules (claims 5-7). However, at the time the invention was made, such was taught by the prior art. For example, Boukobza et al. teach a novel immobilization technique for biomolecules comprising trapping single protein molecules inside lipid vesicles (i.e., a first and a second biomolecule), which are tethered to a supported lipid bilayer via biotin-avidin interaction, wherein the technique overcomes the problem of molecule-surface interaction and wherein the surface-tethered vesicles can be used for experiments on reconstituted membrane proteins and peptides (claims 5 and 6) (12165, column 2, second paragraph, p. 12166, column 1, Fig. 1, p. 12169, column 2, *Conclusion*). It would have been obvious to one of skill in the art, at the time the invention was made, to use the oligonucleotide hybridization as taught by Boxer et al. to tether vesicles to the array of separated lipid bilayers, with a reasonable expectation of success. One of skill in the art would have been motivated to do use

oligonucleotides for tethering in order to obtain expanses with different vesicle composition, each vesicle being encoded by a specific oligonucleotide, as needed. One of skill in the art would have been expected to have a reasonable expectation of success in doing so because the prior art teaches that oligonucleotides are versatile and their use allows for the parallel immobilization of different macromolecules coupled to different nucleic acids (see Niemeyer, Abstract). One of skill in the art would have been motivated to tether vesicles to the array of Boxer et al. because Boukobza et al. teach that vesicles are more suitable than the planar bilayers for studying functional membrane dynamic. With respect to the limitation recited in claim 6, absent evidence of the contrary the protein-loaded vesicles are able to freely move within the expanse. With respect to the limitation recited in claim 7, one of skill in the art would have been motivated to use different second molecules in order to study the reconstitution of several membrane proteins at the same time.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant argues that the secondary references do not remedy the deficiencies of Boxer et al. Additionally, Applicant argues that Boukobza et al. teach tethering via biotin-avidin affinity wherein the entire bilayer expanse is similarly affected, which is in contrast to the claimed invention drawn to an array comprising an oligonucleotide having a surface region specific sequence. With respect to Niemeyer, Applicant argues

that the reference relates to site-specific immobilization of macromolecules on a solid support.

Applicant's argument is acknowledged however, the rejection is maintained for the following reasons:

With respect to the deficiencies of Boxer et al., see above. In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). It is the combination of references which renders the claimed invention *prima facie* obvious.

7. Claims 1-4, 8, 9, 11, and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boxer et al., in view of Shen et al. (PGPUB 2003/0148335, of record).

The teachings of Boxer et al. are applied as above for claims 1-4, 9, 11, and 12.

Boxer et al. do not teach the identity of the biomolcule being determined from the sequence of the oligonucleotide (claim 8). Shen et al. teach the use of oligonucleotide identification tags for assaying the identity of non-nucleic acid targets, wherein the method can be used to identify any non-nucleic acid target associated with any surface (Abstract, p. 2, paragraphs 0009 and 0012, p. 3, paragraph 0017). Shen et al. teach that the oligonucleotide tag can be identified without dissociation by hybridization analysis, wherein the tag is detected by contacting it with an array of complementary

nucleic acids immobilized on a support (p. 3, paragraphs 0021 and 0023). Therefore, it would have been obvious to one of skill in the art, at the time the invention was made, to determine the identity of the biomolecule from hybridization analysis of its attached oligonucleotide with the complementary oligonucleotide present on the bilayer expanse, as taught by Shen et al. with a reasonable expectation of success. One of skill in the art would have been expected to have a reasonable expectation of success in using such a method because the art teaches the successful use of oligonucleotide hybridization in determining the identity of oligonucleotide-tagged biomolecules.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant argues that the secondary reference does not remedy the deficiencies of Boxer et al. Applicant also argues that, in contrast to Shen et al. who teach oligonucleotides for detecting non-nucleic acid targets, the oligonucleotides of the present invention are used for tethering biomolecules to lipid expanses.

Applicant's argument is acknowledged however, the rejection is maintained for the following reasons:

With respect to the deficiencies of Boxer et al., see above. In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Shen et al.

do not have to teach tethering, such is already taught by Boxer et al. Shen et al. was only cited because they demonstrate that the tethering oligonucleotides of Boxer et al. could be used to determine the identity of the tethered biomolecule. Therefore, the combination of Boxer et al. and Shen et al. renders the claimed invention *prima facie* obvious.

8. No claim is allowed. No claim is free of prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILEANA POPA whose telephone number is (571)272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ileana Popa/
Examiner, Art Unit 1633